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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,341	11/21/2000	Jennifa Gosling	19934-000711US	5168

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	23

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/721,341	GOSLING ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 27-51* is/are pending in the application.

4a) Of the above claim(s) *1-24,28-36 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,27,37-41 and 43-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-25 and 27-51* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The Request for Continued Examination (RCE) filed on 12 May 2003 (Paper No. 21) under 37 CFR 1.114 based on parent Application No. 09/721,341 is acceptable and an RCE has been established. An action on the RCE follows.

Status of Application, Amendments and/or Claims

The amendment of 12 May 2003 (Paper No. 12) has been entered in full. Claim 25 is amended and claims 50-51 are added.

Claims 1-24, 28-36, and 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected groups and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10 (28 May 2002).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 25, 27, 37-41, and 43-51 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The rejection of claims 25, 27, 37-41, and 46 under 35 U.S.C. § 102(e) as set forth at pg 9-10 of the previous Office Action (Paper No. 18, 12 February 2003) is *withdrawn* in view of the amended claims (Paper No. 22, 12 May 2003).

2. The rejection of claims 25, 27, 37-41, and 43-49 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pg 7-9 of the previous Office Action (Paper No. 18, 12

February 2003) is *withdrawn* in view of the amended claims and Applicant's persuasive arguments (Paper No. 22, 12 May 2003).

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 18 April 2003 (Paper No. 20) has been considered by the examiner. However, the information disclosure statement fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. Applicant is required to submit a PTO-1449 form in response to this Office Action.

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 25, 27, 37-41, and 43-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the claims recite a method for identifying a modulator of the binding of CCX CKR polypeptide to a chemokine comprising (a) contacting an isolated or recombinant CCX CKR polypeptide having the amino acid sequence as set forth in SEQ ID NO: 2, or a fragment or variant thereof, and the chemokine in the presence of a test compound and (b) comparing the level of binding of the chemokine and the polypeptide in (a) with the level of binding in the absence of the test compound, wherein the CCX CKR polypeptide, fragment or

variant can bind the chemokine in the absence of test compound and the variant has at least 90% sequence identity to SEQ ID NO: 2, the chemokine is selected from the group consisting of ELC, SLC, TECK, BLC, CTACK, mMIP-1γ, and vMIPII, and a decrease in binding indicates that the test compound is an inhibitor of binding and an increase in binding indicates that the test compound is an enhancer of binding.

Applicant's arguments (Paper No. 22, 12 May 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the specification provides guidance on what amino acid positions could potentially be altered and with what amino acids without unduly affecting activity. Applicant indicates that the specification teaches that variants can involve conservative substitutions (pg 7, line 29 to pg 8, line 14). Applicant also contends that Figure 2A provides amino acid sequence alignments between CCX CKR and four other chemokine receptors that illustrate conserved and non-conserved regions between these five receptors. Applicant argues that two of these receptors have binding profiles that overlap with CCX CKR. Applicant submits that those of ordinary skill in the art would know that one logical approach for making variants of SEQ ID NO: 2 that have the binding activity recited in the claims would be to make alterations in non-conserved regions, as such regions appear to tolerate differences. Applicant indicates that screening methods are described in the specification (pg 17, line 16 through pg 18, line 16) that can be utilized to rapidly screen variants that have been formed to identify particular variants that have the desired activity.

Applicant also asserts that the claims as amended do include a structural aspect (e.g., the variant has greater than 90% sequence identity with SEQ ID NO: 2) and a functional aspect (e.g.,

ability to bind a chemokine recited in the claims). Applicant submits that a large quantity of undue experimentation to practice an invention does not necessarily equal undue experimentation. Applicant states that the application provides significant guidance on candidate amino acids that could potentially be altered without adversely affecting activity based on homology comparisons, as well as providing guidance on appropriate substitutions.

Applicant's arguments have been fully considered but are not found to be persuasive. Although the specification may disclose general guidance as to what amino acid positions could potentially be altered without affecting protein activity, the claims recite an infinite number of fragments and variants of SEQ ID NO: 2. The specification teaches that the CCX CKR polypeptides may also be modified, relative to the amino acid sequence of SEQ ID NO: 2, in some manner, e.g. truncated, mutated, derivatized, or fused to other sequences...or contain insertions, deletion or substitutions of amino acid residues relative to SEQ ID NO: 2 (pg 16, lines 28-34; pg 17, line 1). Undue experimentation would be required of the skilled artisan to generate the infinite number of variants recited in the claims and screen the same for activity. Specifically, the problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. Certain positions in the amino acid sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one or ordinary skill in the art to determine, without undue

experimentation, the positions in the CCX CKR protein and DNA which are tolerant to change and the nature and extent of changes that can be made in these positions. Additionally, the broad brush discussion of making and screening for CCX CKR variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the CCX CKR amino acid sequence of SEQ ID NO: 2 is disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error.

Furthermore, the assertion that the disclosed CCX CKR fragments and variants have biological activities and structure similar to known chemokine receptors cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and

TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48). Finally, Murdoch et al. (Blood 95(10): 3032-3043) establish the functional differences between numerous chemokine receptors with similar homology (pg 3032, col 2). For instance, although CCR5 has 49% similarity to CCR3, CCR5 is the major coreceptor in association with CD4 for macrophage-tropic HIV-1 entry permissive cells while CCR3 is predominantly expressed in eosinophils and is involved in the progression of allergic reactions (pg 3035, col 1).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional

information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to make biologically active polypeptide fragment and variants without resorting to undue experimentation to determine what the specific biological activities of the fragments and variants are.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance

presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (Please note that this issue could be overcome by removing the terms "fragment" and "variant" and % identity language from the claims.)

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 25, 27, and 43-49 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 25-27 of copending Application No. 09/686,019. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the instant application and '019 recite a method of identifying a modulator of the binding of CCX CKR to a chemokine comprising

contacting an isolated CCX CKR polypeptide and the chemokine in the presence of a test compound and comparing the level of binding of the chemokine and the polypeptide with the level of binding in the absence of the test compound, wherein a decrease in binding indicates that the test compound is an inhibitor of binding and an increase in binding indicates that the test compound is an enhancer of binding. The genus claims of the '019 application render obvious the species claims of the instant application. The difference between claim 25 of the '019 application and the instant application is that the method of the instant application specifically recites that the CCX CKR polypeptide has the amino acid sequence of SEQ ID NO: 2 or fragments or variants thereof, that the variant has at least 90% sequence identity to SEQ ID NO: 2, and that the chemokine is selected from the group consisting of ELC, SLC, TECK, BLC, CTACK, mMIP-1γ or vMIPII. Claim 25 of the '019 application is silent as to the type of CCX CKR polypeptide and chemokines utilized in the claimed method. Therefore, the claims of the instant application are not patentably distinct over the copending claims in Application No. 09/686,019.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB
Art Unit 1647
July 30, 2003

LORRAINE SPECTOR
PRIMARY EXAMINER